Remarks

This is in response to the Office Action mailed October 22, 2003. Applicant thanks the Examiner for the withdrawal of the rejection under 35 U.S.C. § 112, first paragraph. Claims 2, 3, 6-9, and 12 remain pending. Favorable reconsideration is respectfully requested in light of the amendments and remarks submitted herein.

Claims 2, 3, 6-9 and 12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 95/21944 ("SmithKline") in view of WO 95/24648 ("Hoifodt"). Applicant respectfully traverses this rejection.

The Examiner states that SmithKline discloses methods for conducting differential hybridization whereby genes differentially expressed in diseased tissue as compared with healthy/normal tissue are identified. The Examiner asserts that the level of mRNA expression is also determined in this process. The Examiner notes that SmithKline does not teach immunomagnetically isolating the cells such that nearly 100% specific target cells are obtained, but asserts that Hoifodt remedies this shortcoming by disclosing the use of immunomagnetic methods to not only detect but to isolate target cells in a mixed population of cells. Based on this, the Examiner asserts that it would have been obvious to one of skill in the art to combine the method of Hoifodt with that of SmithKline because one would have been motivated to develop an assay where genes differentially expressed are identified.

Applicant disagrees with the Examiner's construction of the references. Applicant also asserts that the Examine has failed to establish a *prima facie* case of obviousness. In order to establish *prima facie* obviousness, three basic criteria must be met, namely: (1) there must be some suggestion or motivation to combine the references or modify the reference teaching; (2) there must be a reasonable expectation of success; and (3) the reference or references when combined must teach or suggest each claim limitation. Applicant submits that the Office Action failed to state a *prima facie* case of obviousness, and therefore the burden has not properly shifted to Applicant to present evidence of nonobviousness.

SmithKline describes differential hybridization of expressed genes in diseased tissues compared to normal, non-diseased tissues, as well as subtractive hybridization and cloning of genes identified through this procedure. Moreover, they describe

identification of agents (pathogen) causing the disease in the diseased tissues. The techniques used were well known when the present application was filed. However, there are several problems with the method of SmithKline which they have neither specifically described nor remedied and which were well known to a person of skill in the art at the time of the invention.

When comparing diseased tissue, it may be difficult to get corresponding normal cells or tissues from the same individual. However if samples from other individuals are used, the expression pattern may be significantly different, thus confusing expression alterations caused by the disease with expression alterations caused by differences between individuals. Moreover, tissues consist of a mixture of different cell types, and the fraction of the different cell types vary considerably, and is influenced by a high number of known and unknown factors. SmithKline does not describe any enrichment of specific cell types, meaning that they do not know which cell types to target.

Hoifodt discloses a method to detect specific target cells and to enrich the concentration of these cells present in a heterogenous cell population. It is suggested that the cells can be examined for genes at the "DNA, RNA and protein level". The intention in Hoifodt was to examine for known genes since nowhere in the disclosure of Hoifodt is it mentioned that the method was suitable for examining new genes. Furthermore, there is no suggestion or motivation in Hoifodt or SmithKline that would have lead one of skill in the art to the possibility of searching for unknown genes, and certainly not unknown genes expressed differentially in tumor cells present in different host tissues. Thus the citation of the Examiner under item 9 is not correct in that "new genes" are not specifically mentioned.

We agree that the specificity of the process according to Hoifodt may increase the degree of success in a method according to the present invention. However, since 1) Hoifodt does not suggest the study of new genes and 2) SmithKline had well known problems, as mentioned above, one of skill in the art both would not have been motivated to combine SmithKline with Hoifodt and would not have had a reasonable expectation of success had they been combined.

Furthermore, Applicant respectfully asserts that neither Hoifodt, SmithKline, nor the combination thereof would have motivated one of skill in the art to obtain the

Applicant's invention because the features included in Applicant's invention are completely different from the methods disclosed in SmithKline and Hoifodt because Applicant's invention represents a comparison of gene expression patterns of the same type of cells (with the same origin=the primary tumor) found in different tissues, to which the cancer cells have metastasized. By using the tumor cell enrichment procedure Applicant's invention utilized relatively pure populations of target cells, completely different from what SmithKline teaches, thereby avoiding the problems of SmithKline.

Completely different from the teaching of Hoifodt, Applicant's method compares gene expression profiles in tumor cells enriched from different sites/tissues in the same individual. At the time of the invention it was believed that the cells in cancer metastases in such different tissues expressed the same genes as found in the primary tumor, and that when tumor cells did metastasize the metastatic cancer cells would have identical gene expression patterns, irrespective of their site of growth. The Applicant did not agree with that assumption, and the present method thus represents a contradiction of the accepted thinking of the prior art at the time. The present invention surprisingly made it possible to explore this issue by studying gene expression in pure cell populations, not facing the problem wherein various types of normal cells contaminate and confuse the expression pattern and signal intensity. Moreover, because the Applicant compares cells from different sites in the same individual it is now possible to avoid problems related to differences in gene expression in tumors from different individuals, not related to the ability of cancer cells to metastasize.

In conclusion, the teaching of the present application describes a completely novel and inventive approach not previously thought of, and not previously possible to investigate, due to the problems of the prior art described above.

Conclusion

In view of the comments presented herein, favorable reconsideration in the form of a Notice of Allowance is respectfully requested.

Respectfully submitted,

MERCHANT& GOULD P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903
612/332-5300

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John J. Gresens
Reg. No. 33,112
JJG:AMN

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PATENT TRADEMARK OFFICE